INTRODUCTION

As a general rule, superficial myxoid lesions are benign and deep ones are often malignant, with the important exceptions that intramuscular myxoma is deep and myxofibrosarcoma (also called myxoid malignant fibrous histiocytoma) is classically superficial. These latter two lesions are covered in Chapter 21 and are likely to be sampled on needle biopsies, whereas superficial lesions are typically managed by excisional biopsy. The classic myxoid lesions of the genital region (aggressive angiomyxoma and angiomyofibroblastoma) are considered in Chapter 8.

CUTANEOUS MYXOMA AND SUPERFICIAL ANGIOMYXOMA (CUTANEOUS ANGIOMYXOMA)

Myxomas of the dermis and subcutaneous tissue are less well-characterized than the more frequently encountered deep intramuscular myxomas and those arising in the jaw bones and heart. In 1985, Carney et al. described a complex of myxomas, including cutaneous myxomas, spotty pigmentation, and endocrine overactivity—such patients have been subsequently shown to have various mutations in the PRKAR1A gene. In 1988, Allen et al. delineated the clinicopathologic features of histologically similar appearing myxoid lesions of the dermis and subcutaneous tissue which lacked an association with Carney complex. After a critical review of the literature, Allen et al. concluded that the lesions he described, many previously reported and variously named myxoid lesions of the dermis and subcutis, as well as the “cutaneous myxomas” of Carney complex, were all closely related. The term “superficial angiomyxoma” was proposed to encompass both syndromic and sporadic superficial myxomas. Superficial angiomyxomas were unassociated with Carney complex in a subsequent series, so the syndromic ones are presumably rare.

Clinical Features

Allen et al. described three clinical presentations of superficial myxomas. The most common presentation is that of a solitary lesion unassociated with Carney complex, followed by multiple lesions unassociated with
Carney complex, and lastly, lesions associated with the fully expressed Carney complex.

Superficial angiomyxoma/cutaneous myxoma unassociated with Carney complex presents as a painless, slow-growing, solitary skin nodule with a slight male predominance. Lesions arise primarily on the trunk and lower extremity, followed by the head and neck region and arm. They have also been reported in the female and male genital regions.\(^{10}\)

Carney complex\(^1\) includes pigmented skin lesions (lentigines and giant cell blue nevi), endocrine disorders (primary pigmented nodular adrenocortical disease, a variety of stromal tumors of the testis, and growth hormone–producing pituitary adenoma), psammomatous melanocytic schwannoma, and myxomatous tumors (cardiac myxoma, myxoid fibroadenoma of the breast, myxoma of the external ear canal\(^{11}\) and cutaneous myxoma). The disorder is familial and transmitted as an autosomal dominant trait. Females are affected slightly more often than males, and the initial lesions manifest at an early age (mean 18 years). Most patients do not have all of the lesions. However, as the cardiac myxoma and the psammomatous melanocytic schwannoma are the main causes of morbidity and mortality in this disorder,\(^1,12\) it is important to identify patients at risk so that proper evaluation for these potentially lethal tumors can be performed.

Superficial myxomas associated with Carney complex are usually multiple and vary from small sessile papules to large pedunculated lesions. They most commonly occur on the eyelid.\(^1\)

Cutaneous myxomas are benign but local recurrence is common, especially with superficial angiomyxomas containing epithelial components.\(^8\)

**Pathologic Features**

On gross examination, the tumor consists of soft, lobulated nodules, which may appear as polypoid or pedunculated skin lesions. The majority of lesions range between 1 and 5 cm. The cut surface is glistening, mucoid or gelatinous, and gray to white. Incomplete collagenous bands traverse the cut surface, resulting in a nodular configuration.

Microscopically, the process typically involves both the dermis and subcutaneous fat, but, occasionally, only one location is affected (Fig. 20.1). The tumor consists of multiple, variably demarcated angiomyxoid nodules (Fig. 20.2, e-Fig. 20.1). The nodules are composed of a hypo- to moderately cellular population of bland-appearing, short spindled, stellate-shaped (Fig. 20.3, e-Fig. 20.2), and, occasionally, multinucleated cells scattered haphazardly throughout a highly myxoid stroma. Mitotic activity is negligible.

The stroma contains abundant hyaluronic acid-rich matrix that forms microcysts within the nodules and cleft-like spaces at the interface of the nodule with the surrounding tissue. Thin, wavy collagen fibers
This lesion is multilobulated and superficial. On the left part of the field, the tumor has entrapped skin adnexal structures. The vascular element consists of small- to medium-sized, thin-walled, nonarborizing vessels. The vascular density of the nodules varies. Other features observed in superficial angiomyxoma include some perivascular hyalinization, a mixed inflammatory infiltrate (including neutrophils [Fig. 20.4, e-Fig. 20.3] and mast cells), fibrin and hemosiderin deposition, and interstitial hemorrhage.

The tumor lobules have numerous small delicate capillaries.
FIGURE 20.3  Cutaneous myxoma/superficial angiomyxoma. The proliferating cells are small and bland in this example. Occasional examples are more cellular with larger cells (see also e-Figs. 20.2 and 20.3).

Epithelial structures within the tumor nodules (Fig. 20.5), including epidermal cysts with keratinous debris and linear strands of squamous cells emanating from the epidermal surface or from a cyst wall, have been identified in about a third of cases and have contributed to the plethora of names given to superficial angiomyxoma in the past.

The differential diagnosis is summarized in Table 20.1.

FIGURE 20.4  Cutaneous myxomas/superficial angiomyxomas often have abundant intralesional neutrophils.
TABLE 20.1  Differential Diagnosis of Cutaneous Myxoma/Angiomyxoma

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Key Features</th>
<th>Distinction from Cutaneous Myxoma/Angiomyxoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous focal mucinosis</td>
<td>Asymptomatic flesh-colored papule or nodule occurring commonly on face, trunk or extremities; localized collection of mucin in the dermis with an increased number of fibroblasts</td>
<td>Larger, multilobulated, often involves cutaneous and subcutaneous tissue</td>
</tr>
<tr>
<td>Digital mucous cyst</td>
<td>Small and composed of a single mucous cyst of fingers</td>
<td>Smaller, not multilobulated, restricted to digits</td>
</tr>
<tr>
<td>Nerve sheath myxoma</td>
<td>Multilobulated myxoid lesion, S100 protein reactive</td>
<td>Multilobulated myxoid lesion, S100 protein negative</td>
</tr>
<tr>
<td>Neurofibroma</td>
<td>Usually not multilobulated</td>
<td>Multilobulated myxoid lesion, S100 protein negative</td>
</tr>
</tbody>
</table>

(continued)

FIGURE 20.5  Cutaneous myxoma/superficial angiomyxoma showing entrapped adnexal structures.

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Ancillary Investigations

The reported immunoprofile of myxomas is rather broad with variable immunoreactivity reported for vimentin, CD34, muscle-specific and alpha-smooth muscle actins, and, to a lesser extent, for factor XIIIa and S100 protein. In contrast to cardiac myxomas and intramuscular myxomas, they seem to lack GNAS mutations but only a limited number of cases has been tested as of this writing.

SUPERFICIAL ACRAL FIBROMYXOMA

Clinical Features

Fetsch et al. described superficial acral fibromyxoma, and there have been a few subsequent large series, including one that suggests renaming them as “digital fibromyxoma.” Overall, these tumors show a male predominance and arise in mostly middle-aged adults but may affect children and the elderly. Most tumors arise in the hands and feet with a slight predominance in the hand. The vast majority are in the digits.
(fingers and toes), often with a relationship to the nail bed. They sometimes infiltrate fat and occasionally bone. The lesions recur local in about 15% to 25% of cases since they can be infiltrative microscopically.

**Pathologic Features**

Tumors range in size from less than 1 to 2 cm with a median size between 1 and 2 cm and most are well-margined grossly. Microscopically, these lesions are moderately cellular, consisting of stellate to spindled fibroblastic cells set in myxoid to collagenous stroma with numerous slender vessels (Fig. 20.6, e-Figs. 20.10 to 20.15). Some cases display a focal loose storiform growth similar to fibrous histiocytoma (Fig. 20.7). Scattered multinucleated cells are found in about half of cases (see e-Fig. 20.11). Only slight nuclear pleomorphism is detected, mitoses are usually sparse and not atypical, and necrosis is absent. With the exception of mast cells, which are present in most cases (see e-Figs. 20.14 and 20.15), there is minimal inflammation.

**Ancillary Investigations**

Most cases display immunoreactivity for CD34 (e-Fig. 20.16). EMA and CD99 are detected in some cases but not actins, desmin, glial fibrillary acid protein, keratins, HMB-45, MUC4, GFAP, claudin 1, and S100 protein. They lack GNAS mutations.

**MYXOID NEURAL AND NEURAL-LIKE LESIONS**

Lesions in this general category have been called nerve sheath myxoma, neurothekeoma, cellular neurothekeoma, and myxoid neurothekeoma.

The literature is confusing on this family of lesions since the terms neurothekeoma and nerve sheath myxoma were used interchangeably.

**FIGURE 20.6**  **Superficial acral fibromyxoma.** These tumors often proliferate under the nail bed. They are often richly vascular like this tumor, but some examples are more cellular.
in the past when there are actually two entities (Table 20.2), but all are benign and most are superficial. Some, however, are prone to local recurrences based on their infiltrative growth pattern. Remember, however, before considering these more esoteric myxoid lesions, that ordinary neurofibromas are often myxoid (e-Figs. 20.17 to 20.19).

CELLULAR NEUROTHEKEOMA (SEE ALSO CHAPTER 22)

Clinical Features

Cellular neurothekeomas typically present as asymptomatic, solitary, slow-growing, dome-shaped masses that involve the skin and superficial subcutis. Deep involvement of the subcutis is uncommon, and skeletal muscle involvement is rare and largely restricted to the facial region. In a comprehensive series, there was a wide age (i.e., 20 months to 85 years) but most examples presented in the second decade (median age 17 years). Female patients outnumbered males by a margin of almost 2:1. The tumors had a strong predilection for the head (especially the nose, scalp, orbital regions, cheeks, and chin), arms, and upper limb girdles, with more than three-quarters of cases involving these three sites. The trunk, pelvic girdle, legs, hands, and feet were less commonly affected.

Recurrences are relatively uncommon (up to 10%) and mostly represent incompletely excised lesions. Neurothekeomas are benign neoplasms.

Pathologic Features

Since neurothekeomas are typically biopsied by dermatologists, few data are available concerning their gross appearances. Histologically, the tumors can be segregated into three subgroups, based primarily on the
<table>
<thead>
<tr>
<th>Lesion</th>
<th>Clinical Features</th>
<th>Histologic Features</th>
<th>Ancillary Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellular neurothekeoma</td>
<td>Common on head, arms, upper limb girdles, recurrences common (about a third)</td>
<td>Multilobulated, large epithelioid cells</td>
<td>S100 protein−, SOX10−, NKI/C3+</td>
</tr>
<tr>
<td>“Mixed” cellular</td>
<td></td>
<td>Multilobulated, mixture of epithelioid cells and myxoid areas with</td>
<td>S100 protein−, SOX10−, NKI/C3+</td>
</tr>
<tr>
<td>neurothekeoma</td>
<td></td>
<td>spindle cells</td>
<td></td>
</tr>
<tr>
<td>Myxoid cellular</td>
<td></td>
<td>Multilobulated, myxoid areas with spindle cells</td>
<td>S100 protein−, SOX10−, NKI/C3+</td>
</tr>
<tr>
<td>neurothekeoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nerve sheath</td>
<td>Upper extremities, especially hands</td>
<td>Superficial myxoid multinodular masses composed of small</td>
<td>S100 protein+, SOX10+, GFAP+</td>
</tr>
<tr>
<td>myxoma</td>
<td>Head and neck lesions unusual</td>
<td>spindled cells</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Recurrences very common (about half)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

amount of myxoid matrix. Fetsch et al.\textsuperscript{18} regarded examples with ≤10% myxoid matrix as cellular neurothekeomas (Figs. 20.8 and 20.9), tumors with >10% but ≤50% myxoid matrix as mixed-type neurothekeomas, and those with >50% myxoid matrix as cellular myxoid neurothekeomas (Figs. 20.10 and 20.11). Despite the differences in matrix, all tumors have certain features, including (1) epithelioid and spindle cells with relatively abundant, somewhat granular-appearing, eosinophilic cytoplasm; (2) a tendency for tumor cells to form multiple small nodules with whorled and sometimes focal fascicular growth; (3) an association with variable amounts of sclerotic collagen; (4) occasional osteoclast-like giant cells (e-Figs. 20.20 to 20.24); and (5) a similar immunoprofile (see following text). Most have minimal cytologic atypia and mitotic activity, but there are some examples displaying atypical nuclei and scattered mitoses.

Because of overlapping morphology, some regard cellular neurothekeoma as a superficial example of plexiform fibrohistiocytic tumor (see Chapter 22).
FIGURE 20.8 Cellular neurothekeoma. This tumor is composed of multiple nodules that occupy the deep dermis and extend into subcutaneous adipose tissue. The lobules are composed of rounded epithelioid cells.

Ancillary Investigation

On immunohistochemical staining, neurothekeomas nearly invariably express vimentin, NKI/C3, and CD10, and usually MITF, CD99, collagen type IV, NSE, PGP9.5, and CD68. There is variable expression of muscle specific and alpha actin. However, most critically, the consistent lack of S100 protein is the key feature in distinguishing these from true nerve sheath myxomas. Additionally,

FIGURE 20.9 Cellular neurothekeoma. This tumor can appear alarming because of scattered enlarged hyperchromatic cells. Note that there is no mitotic activity.
unlike nerve sheath myxomas, they also lack SOX-10 expression. Lesions also lack GFAP, melan-A, tyrosinase, NFP, CD34, and desmin.

**NERVE SHEATH MYXOMA**

Nerve sheath myxomas are far less common than cellular neurothekeomas. In the past, they have been included within the myxoid subgroup of cellular neurothekeoma, but it is now clear, on the basis of the clinical

**FIGURE 20.10** Myxoid neurothekeoma. Like cutaneous myxoma, it is multilobulated but differs by being less vascular with more basophilic mucinous matrix.

**FIGURE 20.11** Myxoid neurothekeoma. This tumor can show mild cytologic atypia.
demographics, histomorphology, and immunohistochemical findings, that they are a separate clinicopathologic entity. The distinction is clinically relevant, because nerve sheath myxomas are more likely to recur than cellular neurothekeomas (about half of cases).

**Clinical Features**

True nerve sheath myxomas have a peak incidence in the fourth decade, occur with approximately equal frequency in males and females, and have a strong predilection for the extremities (especially the hands), and have a high local recurrence rate when incompletely excised. They only rarely involve the head and neck region.

**Pathologic Features**

Nerve sheath myxomas characteristically form superficial, highly myxoid, multinodular/multilobular masses with a prominent peripheral fibrous border (Fig. 20.12). They contain spindled (Fig. 20.13, e-Fig. 20.25 to 20.27), stellate-shaped, ring-shaped, and epithelioid Schwann cells, and the last are often organized into cords and closely packed syncytial-like aggregates.

**Ancillary Investigations**

The tumor cells are strongly immunoreactive for S100 protein (Fig. 20.14) and SOX10,22 GFAP (see e-Fig. 20.27), NSE, and CD57, and EMA is sometimes detectable in residual perineurial cells at the tumor periphery.19

**FIGURE 20.12 Nerve sheath myxoma.** Like lesions in the cellular neurothekeoma family. These tumors are lobulated and appear quite similar. Often, the individual lobules are less sharply defined than those of cellular neurothekeoma, as seen in e-Figure 20.23. Immunohistochemistry for S100 protein is positive.
SUPERFICIAL MYXOID LESIONS

FIGURE 20.13  Nerve sheath myxoma. Some examples have scattered atypical cells.

FIGURE 20.14  Nerve sheath myxoma. These tumors are S100 protein–reactive, in contrast to neurothekeomas. Immunoperoxidase.

ADIPOSE TISSUE NEOPLASMS THAT MAY HAVE PROMINENT MYXOID AREAS

This category includes lipoblastoma and lipoblastomatosis, spindle cell lipomas, chondroid lipoma, and, the prototype myxoid lesion with lipid droplets, myxoid liposarcoma (addressed in Chapters 15 and 16). These lesions are listed in Table 20.3 and shown in e-Figures. 20.28 to 20.47.
<table>
<thead>
<tr>
<th>Lesion</th>
<th>Clinical Features</th>
<th>Pathologic Features</th>
<th>Ancillary Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipoblastoma</td>
<td>Found in infants, usually involves extremities, poorly</td>
<td>Lobulated lesions with foci with myxoid stroma, prominent vessels, and lipoblasts</td>
<td>PLAG1-HAS2 or PLAG1-COL1A2 rearrangements</td>
</tr>
<tr>
<td></td>
<td>marginated benign lesions</td>
<td>(see e-Figs. 20.26 to 20.30)</td>
<td></td>
</tr>
<tr>
<td>Spindle cell lipoma</td>
<td>Superficial well-marginated benign tumors of neck of</td>
<td>Spindle cell, mast cells, wiry collagen, fat (see e-Figs. 20.31 to 20.40)</td>
<td>CD34+</td>
</tr>
<tr>
<td></td>
<td>middle-aged men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chondroid lipoma</td>
<td>Well-marginated superficial benign lesions of extremities</td>
<td>Epithelioid to chondroid cells, lipoblasts, mature fat (see e-Figs. 20.41 to 20.45)</td>
<td>S100 protein+, t(11;16) (q13;p12–13)</td>
</tr>
<tr>
<td>Myxoid liposarcoma</td>
<td>Deep low- and intermediate-grade malignant lesions of</td>
<td>Myxoid neoplasms with abundant vessels, lipoblasts</td>
<td>TLS-DDIT3 and EWS-DDIT3 rearrangements</td>
</tr>
<tr>
<td></td>
<td>young adults</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-grade myxoid liposarcoma</td>
<td>High-grade variant of myxoid liposarcoma</td>
<td>Cellular neoplasms with obscured vessels, rare lipoblasts</td>
<td>TLS-DDIT3 and EWS-DDIT3 rearrangements</td>
</tr>
<tr>
<td>(round cell liposarcoma)</td>
<td>Deep lesions of young adults</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
REFERENCES


